S/N 10/521,234

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Yonehara et al.	Examiner:	Kade
Serial No.:	10/521,234	Group Art Unit:	1651
Filed:	January 13, 2005	Docket No.:	10873.1574USWO
Title:	METHOD OF DEGRADING PROTEIN USING SULFONIC ACID COMPOUND		

CERTIFICATE UNDER 37 CFR 1.6:
The undersigned hereby certifies that this correspondence is being sent via facsimile to the United States Patent & Trademark Office, Commissioner for Patents (MAIL STOP: APPEAL BRIEF-PATENTS) on August 20, 2008.

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APPELLANTS' BRIEF ON APPEAL

Dear Sir:

This Brief is presented in support of the Notice of Appeal filed January 28, 2008, from the final rejection of Claims 8-15 of the above-identified application, as set forth in the Office Action mailed July 27, 2007 and maintained in the Advisory Action mailed February 7, 2008.

Please charge our Deposit Account No. 50-3478 in the amount of $510.00 to cover the required fee for filing this Brief.

I. REAL PARTY IN INTEREST

The application pending for this appeal has been assigned to Arkray, Inc., of Kyoto, Japan.

II. RELATED APPEALS AND INTERFERENCES

The Assignee, the Assignee's legal representatives, and the Appellants are unaware of any other appeals or interferences that will affect, be directly affected by, or have a bearing on the Board's decision in this Appeal.

III. STATUS OF CLAIMS

Claims 1-7 and 9 are canceled. Claims 8 and 10-15 are pending. Claims 8 and 10-15 are the subject of this Appeal. Appendix A attached herewith provides a copy of the claims in this Appeal.

IV. STATUS OF AMENDMENTS

An Amendment and Response to the final Office Action was filed on December 27, 2007, under 37 C.F.R. § 1.116. In the Amendment and Response filed on December 27, 2007, the subject matter in claim 9 was incorporated into claim 15. By way of Advisory Action mailed February 7, 2008, the Amendment and Response was considered, but deemed as not placing the application in condition for allowance.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 15, the sole independent claim in this application, is directed to a method of measuring a glycated protein. As discussed on page 2, lines 21-24 of the specification, the method of measuring the glycated protein requires treating a sample containing the glycated protein with a protease in the presence of a sulfonic acid compound. The method requires the sulfonic acid compound to be at least one selected from the group consisting of dodecylbenzenesulfonic acid sodium salt, lithium lauryl sulfate, 4-aminoazobenzene-4'-sulfonic acid sodium salt, 4-amino-4'-nitrostilbene-2,2'-disulfonic acid disodium salt, 4,4'-diazidostilbene-2,2'-disulfonic acid disodium salt, N-cyclohexyl-2-aminoethane sulfonic acid, N-cyclohexyl-3-aminopropane sulfonic acid, N-cyclohexyl-2-hydroxy-3-aminopropane sulfonic acid, piperazine-1,4-bis(2-ethane sulfonic acid) and bathophenanthroline sulfonic acid (see page 3, line 32 to page 4, line 3 of the specification).

The method further requires allowing a glycated portion of a glycated protein degradation product obtained by the protease treatment and a fructosyl amino acid oxidase (hereinafter "FAOD") to react with each other (see page 2, lines 33-35 of the specification). The method also requires measuring the redox reaction (see page 2, lines 35-36 of the specification).

The advantageous effects of the method are explained as follows. In conventional methods, glycated proteins are degraded so that FAOD can act on the glycated portion more easily (see page 1, line 33 to page 2, line 1 of the specification). However, proteases usually are substrate specific, and show different degrading activities depending on the substrate to be treated (see page 2, lines 2-3 of the specification). Further, when the target protein is glycated, degradation is hindered due to steric hindrance and the like (see page 2, lines 6-8 of the specification). As such, a protease treatment in the absence of a sulfonic acid compound requires about 6 to 40 hours to sufficiently degrade the glycated protein so as to allow FAOD to act on the glycated portion more easily (see page 3, lines 2-5 of the specification). In contrast, the measuring method of the present claims can shorten the time required for the measurement to about 1/10 to 1/2000 as compared to that of conventional methods (see page 3, lines 7-14 of the specification). Consequently, the measuring method according to the present claims achieves a more efficient and more accurate measurement, which is useful for various tests in clinical medicine (see page 3, lines 14-17 of the specification).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following issues are raised in the final rejection:

1. Whether claim 15 complies with the written description requirement;
2. Whether claims 8 and 12-15 are anticipated by Komori et al. (EP 1 002 874); and
3. Whether claims 8 and 10-15 are obvious over Komori et al. in view of Oshiro et al. (Clin. Biochem. 1982, Vol. 15, No. 1, p.83-88) and further in view of Ishimaru et al. (U.S. Patent No. 6,127,138) and further in view of Johnson et al. (Blood, 1994, Vol. 83, No. 4, p. 1117-1123) and further in view of Yonehara et al. (U.S. Patent No. 6,790,0665).

VII. ARGUMENT

A. Claim 15 complies with the written description requirement

Claim 15 is rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The rejection is rendered moot, as the questioned limitation in

claim 15 has been removed in the Amendment and Response filed on December 27, 2007, under 37 C.F.R. § 1.116. Applicants do not concede the correctness of the rejection.

Reversal of the rejection is respectfully requested.

B. Claims 8 and 12-15 are not anticipated by Komori et al. (EP 1 002 874)

Claims 8 and 12-15 were rejected under 35 U.S.C. § 102(e) as being anticipated by Komori et al. (EP 1 002 874). The rejection is rendered moot, as the subject matter in claim 9 has been incorporated into claim 15 in the Amendment and Response filed on December 27, 2007, under 37 C.F.R. § 1.116. Claims 8 and 12-14 depend from claim 15.

Reversal of the rejection is respectfully requested.

C. Claims 8 and 10-15 are patentable over Komori et al. (EP 1 002 874), Oshiro et al. (Clin. Biochem. 1982, Vol. 15, No. 1, pp. 83-88), Ishimaru et al. (U.S. Patent No. 6,127,138), Johnson et al. (Blood, 1994, Vol. 83, No. 4, pp. 1117-1123) and Yonehara et al. (U.S. Patent No. 6,790,665)

Claims 8-15 were rejected under 35 U.S.C. 103(a) as being unpatentable over Komori et al. (EP 1 002 874) in view of Oshiro et al. (Clin. Biochem. 1982, Vol. 15, No. 1, p.83-88) and further in view of Ishimaru et al. (U.S. Patent No. 6,127,138) and further in view of Johnson et al. (Blood, 1994, Vol. 83, No. 4, p. 1117-1123) and further in view of Yonehara et al. (U.S. Patent No. 6;790,0665). Appellants respectfully contend that the interpretation of the references is unreasonable for the following reasons.

Claim 15 is directed to measuring glycated protein in a sample. Claim 15 requires treating the sample containing the glycated protein with a protease in the presence of a sulfonic acid compound. Claim 15 further requires the sulfonic acid compound to be at least one selected from the group consisting of dodecylbenzenesulfonic acid sodium salt, lithium lauryl sulfate, 4-aminoazobenzene-4'-sulfonic acid sodium salt, 4-amino-4'-nitrostilbene-2,2'-disulfonic acid disodium salt, 4,4'-diazidostilbene-2,2'-disulfonic acid disodium salt, N-cyclohexyl-2-aminoethane sulfonic acid, N-cyclohexyl-3-aminopropane sulfonic acid, N-cyclohexyl-2-hydroxy-3-aminopropane sulfonic acid, piperazine-1,4-bis(2-ethane sulfonic acid) and bathophenanthroline sulfonic acid.

When the sulfonic acid compounds as required by claim 15 are used along with the protease, the time required for sufficiently degrading the glycated protein so as to allow FAOD

to act on the glycated portion easily is shortened significantly. As a result, the accuracy of measurement is improved considerably (see page 3, lines 10-14 of the specification).

On the other hand, the references provide no reason to select at least one of the sulfonic acids required by claim 15 and use the selected sulfonic acids with a protease to treat a sample containing the glycated protein, nor any reason to expect that a protease could be combined with the specific sulfonic acids of claim 15 and achieve the benefit of superior degradation of glycated protein.

More particularly, Komori et al. teach a method involving a hemolysis treatment, a pretreatment with tetrazolium compound, a protease treatment, an FAOD treatment and a POD redox treatment.

Komori et al. teach that the hemolysis treatment can involve conventional methods using a surfactant (paragraph [0043]). The reference gives examples of non-ionic surfactants which include polyoxyethylene-p-t-octylphenyl ether (e.g. Triton series surfactants), polyoxyethylene sorbitan alkyl ester (e.g. Tween series surfactants) and polyoxyethylene alkyl ether (e.g. Brij series surfactants) (paragraph [0044]). The reference further gives specific examples that include Triton X-100, Tween-20, Brij 35, and the like (paragraph [0044]). However, none of these surfactants corresponds to the sulfonic acid compounds required by claim 15. Moreover, although the reference teaches that the hemolysis treatment can be performed simultaneously with the protease treatment (paragraph [0061]), it can be clearly understood from the above description that Komori et al. use the surfactants for cell permeabilization and cell lysis, not for enhancing protease degradation. Furthermore, one would not expect from the above description that the surfactants used by Komori et al. would lead to superior degradation of glycated protein.

Komori et al. further teach that the POD redox treatment involves a redox reaction using POD and a color-developing substrate (paragraph [0056]). Komori et al. teach that examples of the color-developing substrate include a substrate in which trinder's reagent and 4-aminoantipyrine are combined (paragraph [0057]). The reference teaches that in place of aminoantipyrine, vanillin diamine sulfonic acid may be used (paragraph [0057]). However, vanillin diamine sulfonic acid does not correspond to any of the sulfonic acid compounds required by claim 15. Moreover, although the reference teaches that the POD redox treatment can be performed simultaneously with the protease treatment (paragraph [0061]), it can be

clearly understood from the above description that Komori et al. use the vanillin diamine sulfonic acid for color-development, not for enhancing protease degradation. Furthermore, one would not expect from Komori et al. that the vanillin diamine sulfonic acid used by the reference would lead to superior degradation of glycated protein.

From the above, it is clear that nothing in Komori et al. teaches or suggests treating a sample containing the glycated protein with a protease in the presence of one or more sulfonic acid compounds selected from the group required in claim 15. It is also clear that nothing in Komori et al. would guide a skilled artisan to use the sulfonic acids required by claim 15 with a protease with an expectation to achieve superior degradation of glycated protein. Accordingly, claim 15 is patentable over Komori.

The rejection contends that Johnson et al. teach formation of 2,4-dinitrophenyl-S-glutathione to lower the glutathione levels in the erythrocytes, and thus it would have been obvious to use 2,4-dinitrophenol (a dinitrophenol derivative) in the method according to Komori et al. to eliminate any reducing agent such as glutathione (GSH) which can react with hydrogen peroxide and interfere with the measurement of the amount of glycated protein. Applicants respectfully contend that the rejection improperly uses hindsight in assessing the relevance of Johnson et al.

More particularly, although Komori et al. mention in paragraphs [0002-0005] in describing conventional methods that GSH was thought to be the cause of the problem, Komori et al. further note in paragraph [0011] that "[a]s a result of extensive studies, the inventors found that the cause of the problems in the conventional methods was not that the influence of the low molecular weight reducing substances such as the above-mentioned GSH and AsA were not eliminated, but that the influence of high molecular weight reducing substances such as proteins or the like were not eliminated." As such, contrary to the rejection's position, one in fact would not have been motivated to use Johnson et al.'s CDNB to eliminate GSH in view of the above description.

Moreover, Johnson et al. is directed to studying chronic hemolysis found in G6PD^{Wayne}. While one study involves using 1-chloro-2,4-dinitrobenzene (CDNB) to lower GSH levels in normal red blood cells to determine the role of GSH in protecting membrane proteins against oxidation and maintaining membrane stability (page 1120, col. 2), there is no experimental work

or detailed explanation that would lead one to expect with any reasonable degree of certainty that the use of CDNB would be appropriate with systems that measure the oxidation of glycated proteins. To the contrary, Johnson et al. note that when GSH was reduced to undetectable levels by addition of CDNB, there was extensive hemoglobin oxidation in the cells (page 1120, col. 2). Thus, one would question whether, after adding CDNB to Komori et al.'s system before the redox reaction with FAOD, the hydrogen peroxide generated from the glycated proteins that have been extensively oxidized by the presence of CDNB would accurately reflect the actual amount of glycated protein. Accordingly, claim 15 is patentable over Komori et al. and Johnson et al. taken alone, or together.

Ishimaru et al. do not cure the deficiencies of Komori et al. and Johnson et al. Although Ishimaru et al. disclose the use of metalloprotease, nothing in Ishimaru et al. teaches or suggests the use of a sulfonic acid compound selected from the group required by claim 15 during the protease treatment, nor any reason to expect that the sulfonic acid compounds required by claim 15 could be used with a protease to achieve superior degradation of glycated protein.

The rejection relies on Oshiro and Yonehara for the use of sodium lauryl sulfate. The rejection's reliance is moot, as claim 15 does not require the use of sodium lauryl sulfate.

Moreover, Oshiro et al. teach a method of using SLS for the measurement of hemoglobin, and fails to teach or suggest measuring specifically the amount of glycated hemoglobin in a sample using protease and FAOD. The reference even notes that the method does not need oxidative agents. In addition, nothing in Oshiro et al. provides any reason to use the sulfonic acids as required by claim 15 together with a protease, let alone any reason to expect that the sulfonic acids required by claim 15 used with a protease would lead to superior degradation of glycated protein. Furthermore, Yonehara et al. disclose that the SLS method involves the addition of both SLS and a strong alkali in a sample, and actually discourages the use of such a method since the addition of these reagents influences enzymatic measurement systems.

Accordingly, for at least the above reasons, claim 15 is patentable over Komori et al., Oshiro et al., Ishimaru et al., Yonehara et al and Johnson et al., taken alone or together. Claims 8 and 10-14 are also patentable over the references since they depend from claim 15 that is allowable. Reversal of the rejection is respectfully requested.

VIII. CONCLUSION

Appellants submit that the rejections of claims 8 and 10-15 are untenable for the reasons set forth above and should be reversed.

Please charge any additional fees or credit any overpayment to Hamre, Schumann, Mueller & Larson Deposit Account No. 50-3478.

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Respectfully submitted,

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APPENDIX A - PENDING CLAIMS

1-7. (Canceled)

8. (Previously Presented) The method according to claim 15, wherein the protease treatment is carried out in the presence of the sulfonic acid compound and a nitro compound.

9. (Canceled)

10. (Previously Presented) The method according to claim 8, wherein the nitro compound is at least one selected from the group consisting of 2,4-dinitrophenol, 2,5-dinitrophenyl, 2,6-dinitrophenyl, 4,6-dinitro-2-methyl phenol, 2-amino-4-nitrophenol, 2-amino-5-nitrophenol, 2-amino-4-nitrophenol, p-nitrophenol, 2,4-dinitroaniline, p-nitroaniline, sodium nitrite, potassium nitrite, 4-amino-4'-nitrostilbene-2,2'-disulfonic acid disodium salt and nitrobenzene.

11. (Previously Presented) The method according to claim 15, wherein the protease is metalloproteinase.

12. (Previously Presented) The method according to claim 15, wherein the redox reaction is measured by determining an amount of hydrogen peroxide generated by the reaction of the glycated portion of the glycated protein degradation product and the fructosyl amino acid oxidase.

13. (Original) The method according to claim 12, wherein the amount of the hydrogen peroxide is determined by using an oxidase to reduce the generated hydrogen peroxide and oxidize a substrate that develops color by oxidation and measuring a degree of the color that the substrate has developed.

14. (Original) The method according to claim 13, wherein the degree of the color is measured by measuring an absorbance at a wavelength for detecting the substrate.

15. (Previously Presented) A method of measuring a glycated protein, the method comprising:

treating a sample containing the glycated protein with a protease in the presence of a sulfonic acid compound,

allowing a glycated portion of a glycated protein degradation product obtained by the protease treatment and a fructosyl amino acid oxidase to react with each other, and

measuring the redox reaction,

wherein the sulfonic acid compound is at least one selected from the group consisting of dodecylbenzenesulfonic acid sodium salt, lithium lauryl sulfate, 4-aminoazobenzene-4'-sulfonic acid sodium salt, 4-amino-4'-nitrostilbene-2,2'-disulfonic acid disodium salt, 4,4'-diazidostilbene-2,2'-disulfonic acid disodium salt, N-cyclohexyl-2-aminoethane sulfonic acid, N-cyclohexyl-3-aminopropane sulfonic acid, N-cyclohexyl-2-hydroxy-3-aminopropane sulfonic acid, piperazine-1,4-bis(2-ethane sulfonic acid) and bathophenanthroline sulfonic acid.

APPENDIX B - EVIDENCE

Not applicable

APPENDIX C - RELATED PROCEEDINGS

Not applicable